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(56) References cited:
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EP-A- 0 313 397
EP-A- 0 354 777
GB-A- 2 186 874

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The file contains technical information submitted after the application was filed and not included in this specification

EP 0 486 666 B1

Description

The present invention is concerned with new chemical compounds, their preparation, pharmaceutical formulations containing them and their use in medicine, particularly the prophylaxis and treatment of migraine.

Receptors which mediate the actions of 5-hydroxytryptamine (5-HT) have been identified in mammals in both the periphery and the brain. According to the classification and nomenclature proposed in a recent article (Bradley et at, Neuropharmac., 25, 563 (1986), these receptors may be classified into three main types, viz. "5-HT_1-like", 5-HT_2 and 5-HT_3. Various classes of compounds have been proposed as 5-HT agonists or antagonists for therapeutic use, but these have not always been specific to a particular type of 5-HT receptor. European Patent Specification 0313397 describes a class of 5-HT agonists which are specific to a particular type of "5-HT_1-like" receptor and are effective therapeutic agents for the treatment of clinical conditions in which a selective agonist for this type of receptor is indicated. For example, the receptor in question mediates vasoconstriction in the carotid vascular bed and thereby modifies blood flow therein. The compounds described in the European specification are therefore beneficial in the treatment or prophylaxis of conditions wherein vasoconstriction in the carotid vascular bed is indicated, for example, migraine, a condition associated with excessive dilation of the carotid vasculature. However, it is within the scope of the earlier application that the target tissue may be any tissue wherein action is mediated by "5-HT_1-like" receptors of the type referred to above.

EP-A-354777 describes a class of compounds having an indole ring structure substituted at the 3-position by a piperidine group and at the 5-position by a 2-sulfonylaminoethyl group i.e. a sulphonamate group. These indole derivatives exhibit 5-HT_1-like receptor agonism.

A broader class of indole derivative is described in EP-A-303506. These compounds are substituted at the 3-position of the indole ring by a piperidine or 1,2,3,6-tetrahydro-4-pyridinyl group and at the 5-position by a sulphonamide or carboxamide group. They are also said to exhibit 5-HT_1-like receptor agonism.

GB-A-2186874 describes indole derivatives substituted at the 3-position by an aminoalkyl group and at the 5-position by a sulphonamide or carboxamide group. These compounds are said to have selective vasoconstrictor activity.

We have now found a further class of compounds having exceptional "5-HT_1-like" receptor agonism and excellent absorption following oral dosing. These properties render the compounds particularly useful for certain medical applications, notably the prophylaxis and treatment of migraine, cluster headache and headache associated with vascular disorders, hereinafter referred to collectively as "migraine".

According to the first aspect of the present invention, therefore, there is provided a compound N,N-dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-yl-methyl)-1H-indol-3-yl]ethylamine in either its (S) or (R) form or as a mixture thereof in any proportions, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof. The salts and solvates of these compounds, for example, the hydrate maleates, are particularly preferred.

Physiologically acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to the parent, i.e. basic, compounds. Such salts must clearly have a physiologically acceptable anion. Suitable physiologically acceptable salts of the compounds of the present invention include those derived from acetic, hydrochloric, hydrobromic, phosphoric, malic, maleic, fumaric, citric, sulphuric, lactic, or tartaric acid. The succinate and chloride salts are particularly preferred for medical purposes. Salts having a non-physiologically acceptable anion are within the scope of the invention as useful intermediates for the preparation of physiologically acceptable salts and/or for use in non-therapeutic, for example, in vitro, situations.

According to a second aspect of the present invention, there is provided a compound of the invention as hereinbefore defined or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof for use as a therapeutic agent, specifically as a "5-HT_1-like" receptor agonist, for example, as a carotid vasoconstrictor in the prophylaxis and treatment of migraine. As indicated, however, target organs for the present compounds other than the carotid vasculature are within the scope of the present invention.

The amount of a compound of the invention as hereinbefore defined, or a salt or solvate thereof, which is required to achieve the desired biological effect will depend on a number of factors such as the specific compound, the use for which it is intended, the means of administration, and the recipient. A typical daily dose for the treatment of migraine may be expected to lie in the range 0.01 to 5mg per kilogram body weight. Unit doses may contain from 1 to 100mg of a compound of the invention as hereinbefore defined, for example, ampoules for injection may contain from 1 to 10mg and orally administrable unit dose formulations such as tablets or capsules may contain from 1 to 100mg. Such unit doses may be administered one or more times a day, separately or in multiples thereof. An intravenous dose may be expected to lie in the range 0.01 to 0.15mg/kg and would typically be administered as an infusion of from 0.0003 to 0.15mg per kilogram per minute. Infusion solutions suitable for this purpose may contain from 0.01 to 10mg/ml.

When the active compound is a salt or solvate of a compound of the invention, the dose is based on the cation (for salts) or the unsolvated compound.

Hereinafter references to "compound(s) of the invention" will be understood to include compounds of the invention as hereinbefore defined, physiologically acceptable salts and solvates thereof.

According to a third aspect of the present invention, therefore, there are provided pharmaceutical compositions comprising, as active ingredient, at least one compound of the invention and/or a pharmacologically acceptable salt or solvate thereof together with at least one pharmaceutical carrier or excipient. These pharmaceutical compositions may be used in the prophylaxis or treatment of clinical conditions for which a "5-HT_1-like" receptor agonist is indicated, for example, migraine. The carrier must be pharmaceutically acceptable to the recipient and must be compatible with, i.e. not have a deleterious effect upon, the other ingredients in the composition. The carrier may be a solid or liquid and is preferably formulated with at least one compound of the invention as a unit dose formulation, for example, a tablet which may contain from 0.05 to 95% by weight of the active ingredient. If desired, other physiologically active ingredients may also be incorporated in the pharmaceutical compositions of the invention.

Possible formulations include those suitable for oral, sublingual, buccal, parenteral (for example, subcutaneous, intramuscular, or intravenous), rectal, topical and intranasal administration. The most suitable means of administration for a particular patient will depend on the nature and severity of the condition being treated and on the nature of the active compound, but, where possible, oral administration is preferred.

Formulations suitable for oral administration may be provided as discrete units, such as tablets, capsules, cachets, or lozenges, each containing a predetermined amount of the active compound; as powders or granules; as solutions or suspensions in aqueous or non-aqueous liquids; or as oil-in-water or water-in-oil emulsions.

Formulations suitable for sublingual or buccal administration include lozenges comprising the active compound and, typically, a flavoured base, such as sugar and acacia or tragacanth, and pastilles comprising the active compound in an inert base, such as gelatin and glycerin or sucrose and acacia.

Formulations suitable for parenteral administration typically comprise sterile aqueous solutions containing a predetermined concentration of the active compound; the solution is preferably isotonic with the blood of the intended recipient. Although such solutions are preferably administered intravenously, they may also be administered by subcutaneous or intramuscular injection.

Formulations suitable for rectal administration are preferably provided as unit-dose suppositories comprising the active ingredient and one or more solid carriers forming the suppository base, for example, cocoa butter.

Formulations suitable for topical or intranasal application include ointments, creams, lotions, pastes, gels, sprays, aerosols and oils. Suitable carriers for such formulations include petroleum jelly, lanolin, polyethylene glycols, alcohols, and combinations thereof. The active ingredient is typically present in such formulations at a concentration of from 0.1 to 15% w/w.

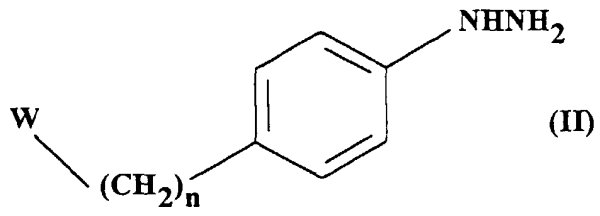
The formulations of the invention may be prepared by any suitable method, typically by uniformly and intimately admixing the active compound(s) with liquids or finely divided solid carriers, or both, in the required proportions and then, if necessary, shaping the resulting mixture into the desired shape.

For example, a tablet may be prepared by compressing an intimate mixture comprising a powder or granules of the active ingredient and one or more optional ingredients, such as a binder, lubricant, inert diluent, or surface active dispersing agent, or by moulding an intimate mixture of powdered active ingredient and inert liquid diluent.

Aqueous solutions for parenteral administration are typically prepared by dissolving the active compound in sufficient water to give the desired concentration and then rendering the resulting solution sterile and isotonic.

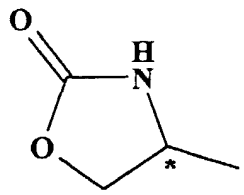
Thus, according to a fourth aspect of the present invention, there is provided the use of a compound of the invention in the preparation of a medicament for the prophylaxis or treatment of a clinical condition for which a "5-HT_1-like" receptor agonist is indicated, for example, migraine.

According to a fifth aspect of the invention, compounds of the invention may be prepared by reacting a compound of formula (II) (isolated or in situ - infra).

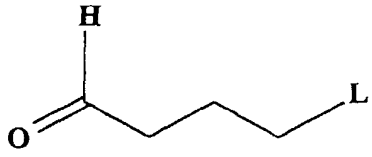


(II)

wherein n is 1 and W is a group



and the chiral centre * is in its (S) or (R) form or is a mixture thereof in any proportions, with a compound of formula (III)



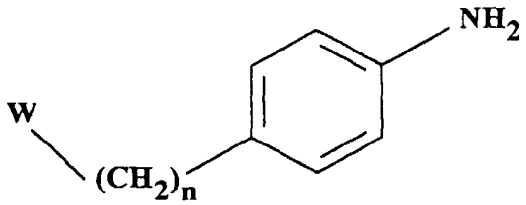
(III)

or a carbonyl-protected form thereof, such as the dimethyl or diethyl acetal, wherein L is a suitable leaving group, such as chlorine, or a protected amino group, either of which may be converted in situ to an amino group or a dimethylamino group, or is - NR^1R^2 where R^1 and R^2 are each methyl or hydrogen. The reaction is typically carried out by refluxing the compounds in a polar solvent system, for example, ethanol/water, dilute acetic acid, or water in the presence of an acidic ion exchange resin, for example, 'Amberlyst 15'.

Standard N-alkylation methods may be used to convert compounds wherein R^1 and R^2 are hydrogen to corresponding compounds of the invention wherein R^1 and R^2 are each methyl.

Compounds of the invention may be prepared from the corresponding compound wherein $R^1 = R^2 = H$ by methods of N,N-dialkylation well known to those skilled in the art, for example, by treatment with the appropriate aldehyde in the presence of a reducing system, for example, sodium cyanoborohydride/ acetic acid, in a polar solvent, such as methanol.

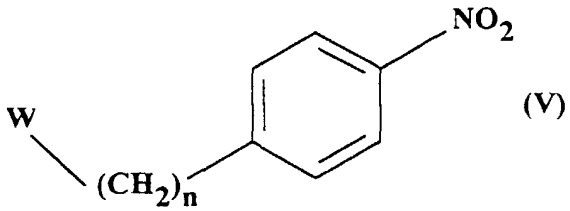
Hydrazines of formula (II) may be prepared from the corresponding aniline of formula (IV)



(IV)

wherein n and W are as hereinbefore defined, by diazotisation followed by reduction. Diazotisation is typically carried out using sodium nitrite/c.HCl and the resulting diazo product reduced in situ using, for example, tin(II) chloride/c.HCl. The resulting hydrazine may be isolated or converted to a compound of the invention in situ.

Anilines of formula (IV) may be prepared by reduction of the corresponding p-nitro compound of formula (V)

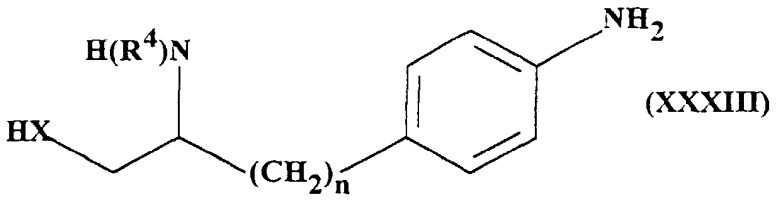


(V)

wherein n and W are as hereinbefore defined, typically by catalytic hydrogenation using, for example, Pd/C in a polar solvent system, such as an acidified mixture of ethanol, water and ethyl acetate.

Anilines of formula (IV) wherein W is as hereinbefore defined may also be prepared by cyclising a compound of

formula (XXXIII)

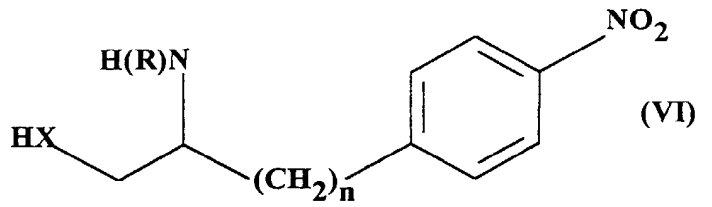


(XXXIII)

wherein n is 1 and X is oxygen and R^4 is $-CO_2R^5$ where R^5 is C_{1-4} alkyl, typically by heating in the presence of a base, such as sodium methoxide.

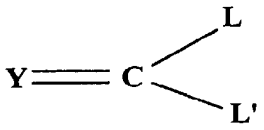
Compounds of formula (XXXIII) may be prepared by reducing a corresponding C_{1-4} alkyl ester using, for example, sodium borohydride, in a polar solvent system, such as ethanol/water, at 0° C. The ester may be prepared by esterifying the corresponding carboxylic acid using, for example, the appropriate alcohol and HCl or by reducing the corresponding p-nitro compound, for example, by catalytic hydrogenation. Both the acid and the p-nitro compound may be prepared from the corresponfling p-nitroaminoacid, the acid by N-alkoxycarbonylation using, for example, R_5 OCOCl where R^5 is as hereinbefore defined, followed by reduction of the nitro group, for example, by catalytic hydrogenation, or by reduction of the nitro group followed by N-alkoxycarbonylation, and the p-nitro compound by N-alkoxycarbonylation (as for the acid) followed by esterification using, for example, the appropriate alcohol and HCl, or by esterification followed by N-alkoxycarbonylation. The p-nitroaminoacid may be obtained commercially or prepared from readily available starting materials by methods known to those skilled in the art or obtainable from the chemical literature, for example, by p-nitration of the corresponding aminoacid using, for example, $c.H_2SO_4/c.HNO_3$ at 0°C.

p-Nitro compounds of formula (V) may be prepared by reacting a compound of formula (VI)



(VI)

wherein n and X are as hereinbefore defined and R is hydrogen, with a compound of formula (VII)



(VII)

(VII)

wherein Y is oxygen and L and L', which may be the same or different, are suitable leaving groups, for example, chlorine, ethoxy, trichloromethyl, trichloromethoxy, or imidazoyl, for example, in the case where L = L' = chlorine, in a non-polar solvent, such as toluene, in the presence of a base, for example, potassium hydroxide.

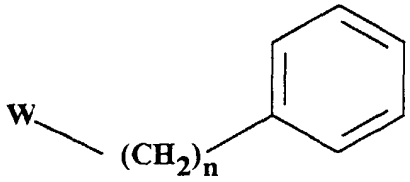
Compounds of formula (VI) may be prepared by ring-opening a compound of formula (V) wherein n and W are as hereinbefore defined, for example, by refluxing in 2N aqu. KOH.

Compounds of formula (VI) may be prepared by esterification of the corresponding carboxylic acid, typically by treatment with thionyl chloride and an appropriate alcohol at -10°C, followed by reduction of the ester using, for example, sodium borohydride, in a polar solvent system, such as ethanol/water, at 0°C. The acid may be obtained commercially or prepared from readily available starting materials by methods known to those skilled in the art or obtainable from the chemical literature, for example, by p-nitration of the corresponding aminoacid using, for example, $c.H_2SO_4/c.HNO_3$

at 0°C.

Compounds of formula (III) and (VII) may be obtained commercially or prepared from readily available starting materials by methods known to those skilled in the art or obtainable from the chemical literature.

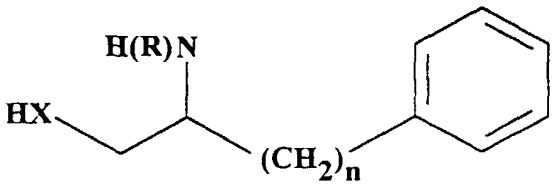
p-Nitro compounds of formula (V) may also be prepared by p-nitration of a compound of formula (XXXVI)



(XXXVI)

wherein n and W are as hereinbefore defined, using, for example, $c.H_2SO_4/c.HNO_3$ at 0°C.

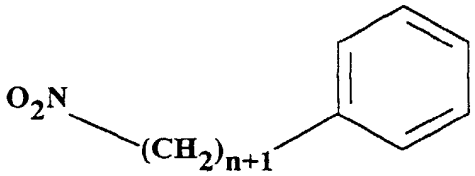
Compounds of formula (XXXVI) may be prepared by reacting a compound of formula (XXXVII)



(XXXVII)

wherein n, R and X are as hereinbefore defined, with a compound of formula (VII) wherein Y, L and L' are as hereinbefore defined, typically in the presence of a base, for example, potassium hydroxide, in a non-polar solvent, such as toluene.

Compounds of formula (XXXVII) may be prepared by reducing the corresponding nitro compounds, typically by catalytic hydrogenation using, for example, Pd/C in a polar solvent, such as ethanol. The nitro compound corresponding to the compound of formula (XXXVII) may be prepared by reacting a compound of formula (XXIV)

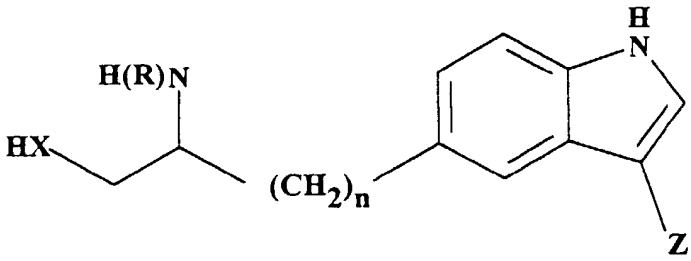


(XXIV)

wherein n is as hereinbefore defined, with paraformaldehyde in a polar aprotic solvent, such as DMF, in the presence of a base, for example, sodium methoxide, at 0°C, or by esterification of the corresponding carboxylic acid, typically by treatment with thionyl chloride and an appropriate alcohol at -10°C, followed by reduction of the ester group using, for example, sodium borohydride, in a polar solvent system, such as ethanol/water at 0°C.

The compound of formula (XXIV) and the acid may be obtained commercially or prepared from readily available starting materials by methods known to those skilled in the art or obtainable from the chemical literature.

Compounds of the invention may also be prepared by reacting a compound of formula (XV)

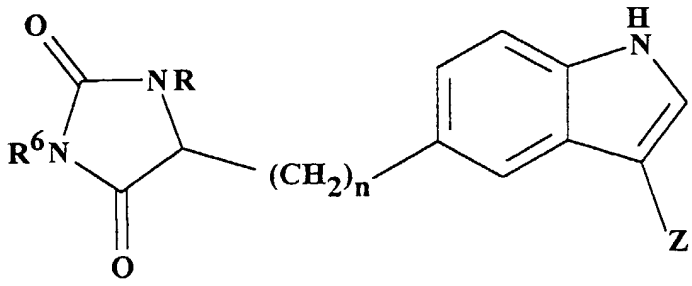


(XV)

wherein n, R and X are as hereinbefore defined and Z is a group $-CH_2CH_2NR^1R^2$ wherein R^1 and R^2 are each methyl

with a compound of formula (VII) wherein Y, L and L' are as hereinbefore defined, for example, in the case where L = L' = ethoxy, by heating in the presence of a base, for example, potassium carbonate.

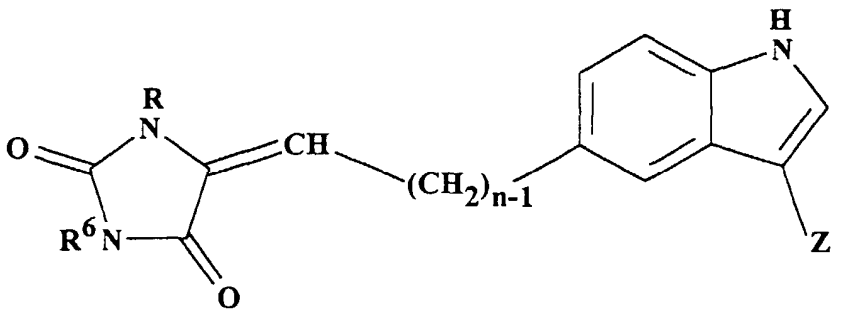
Compounds of formula (XV) may be prepared by esterification of the corresponding carboxylic acid, typically by treatment with thionyl chloride and an appropriate alcohol at -10°C, followed by reduction of the ester using, for example, sodium borohydride, in a polar solvent system, such as ethanol/water, at 0°C. The acid may be prepared by ring-opening a compound of formula (XVI)



(XVI)

wherein n, R and Z are as hereinbefore defined and R^6 is hydrogen or benzyl, typically by refluxing in water in the presence of a base, for example, barium hydroxide.

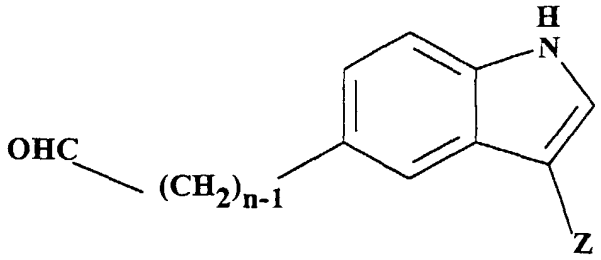
Compounds of formula (XVI) may be prepared by reducing a compound of formula (XVII)



(XVII)

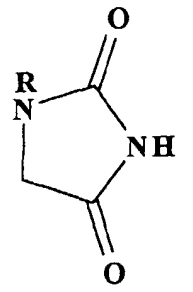
wherein n, R, R^6 and Z are as hereinbefore defined typically by catalytic hydrogenation using, for example, Pd/C in a polar solvent system, such as ethanol/water. Alternatively, an enantioselective reducing agent, such as Rh(cod)(di-pamp)$^+$ BF_4^- (JCS, Chem. Comm. 275 (1991)), may be used to reduce the double bond and thereby introduce a chiral centre at the 4-position of the dioxoimidazole ring.

Compounds of formula (XVII) may be prepared by reacting a compound of formula (XVIII)



(XVIII)

wherein n and Z are as hereinbefore defined, with, in the case where R^6 is to be hydrogen, a compound of formula (X)

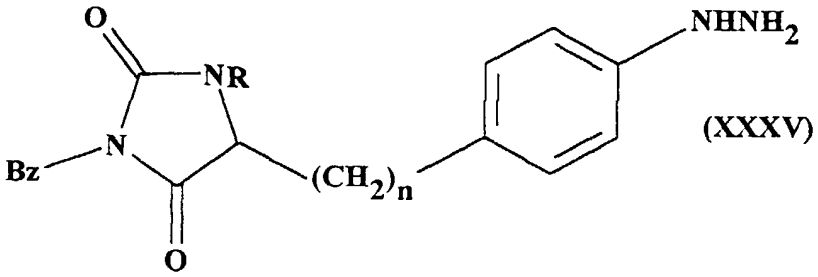


(X)

wherein R is as hereinbefore defined, typically by heating in glac. acetic acid in the presence of ammonium acetate.

Compounds of formula (XVIII) may be prepared by the reduction/ hydrolysis of the corresponding nitrile, typically using Raney nickel and sodium hypophosphite in a mixture of water, acetic acid and pyridine.

Compounds of formula (XVI) wherein R^6 is benzyl and Z is as hereinbefore defined may be prepared by reacting a compound of formula (XXXV)

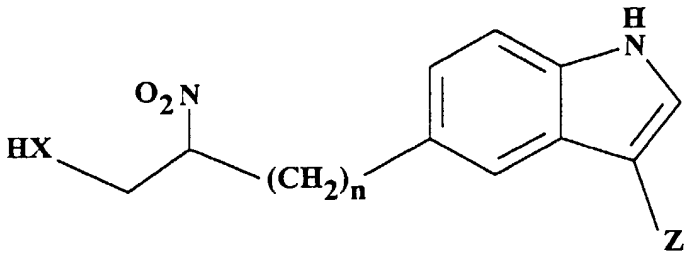


(XXXV)

wherein n and R are as hereinbefore defined, with a compound of formula (III) wherein L is as hereinbefore defined, typically using the reaction conditions described above for the reaction of (II) with (III).

Hydrazines of formula (XXXV) may be prepared from the corresponding aniline, typically using the reaction conditions described above for the conversion of (IV) to (II). The aniline may be prepared by reducing the corresponding p-nitro compound, typically using the reaction conditions described above for the conversion of (V) to (IV). The p-nitro compound may be prepared by reacting the corresponding p-nitroaminoacid with benzyl isocyanate in the presence of base, for example, potassium hydroxide, in a polar solvent, such as water. The p-nitroaminoacid may be obtained commercially or prepared from readily available starting materials by methods known to those skilled in the art or obtainable from the chemical literature, for example, by p-nitration of the corresponding aminoacid using, for example, $c.H_2SO_4/c.HNO_3$ at 0°C.

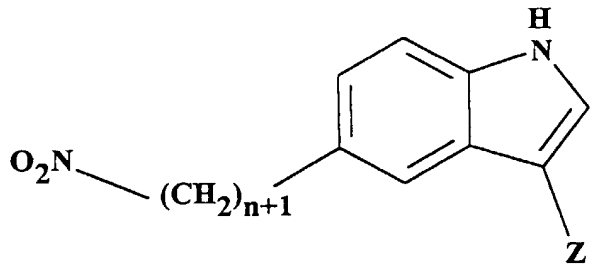
Compounds of formula (XV) may be prepared by reducing a compound of formula (XX)



(XX)

wherein n, X and Z are as hereinbefore defined, typically by catalytic hydrogenation using, for example, Pd/C in a polar solvent, such as ethanol.

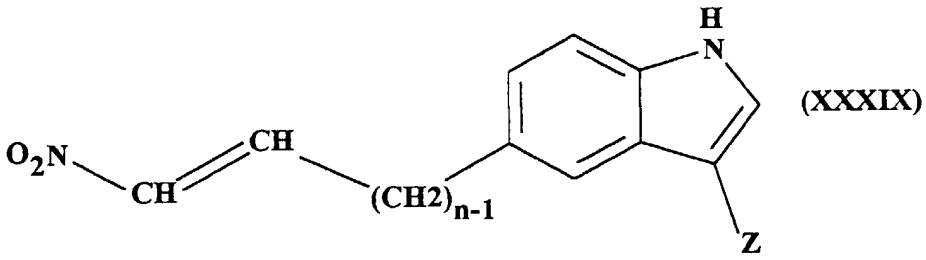
Compounds of formula (XX) may be prepared by reacting a compound of (XXI)



(XXI)

wherein n and Z are as hereinbefore defined, with paraformaldehyde in a polar aprotic solvent, such as DMF, in the presence of a base, for example, sodium methoxide, at 0°C.

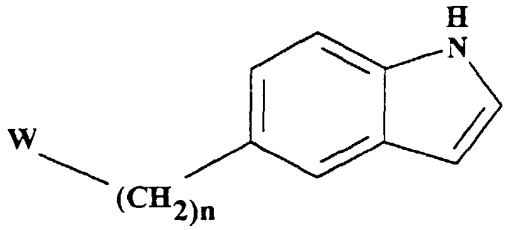
Compounds of formula (XXI) may be prepared from a compound of formula (XXXIX)



(XXXIX)

wherein n and Z are as hereinbefore defined, using for example, sodium borohydride and 40% W/V aqu. NaOH in a polar aprotic solvent, such as acetonitrile at 0°C. Compounds of formula (XXXIX) may be prepared from a compound of formula (XVIII) wherein n and Z are as hereinbefore defined by treating with nitromethane in the presence of ammomium acetate.

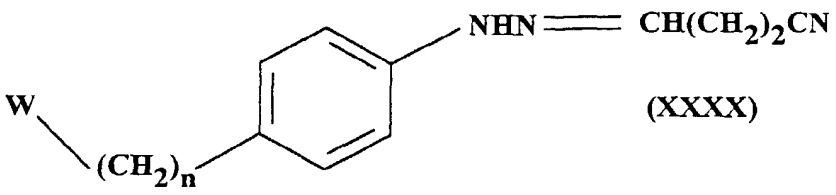
Compounds of the invention may also be prepared from a compound of formula (XXXI)



(XXXI)

wherein n and W are as hereinbefore defined, by methods known to those skilled in the art or obtainable from the chemical literature, for example, by treatment with $(COL)_2$, where L is a suitable leaving group, for example, chlorine, to give the corresponding 3-COCOL compound which may then be treated with HNR^1R^2, where R^1 and R^2 are as hereinbefore defined, and reduced using, for example, lithium aluminium hydride. Alternatively, the compound of formula (XXXI) may be treated with CH_2O/KCN to give the corresponding 3-cyanomethyl compound which may then be catalytically hydrogenated over Raney nickel in the presence of HNR^1R^2 as hereinbefore defined.

The aforementioned 3-cyanomethyl compound may also be prepared by cyclising a compound of formula (XXXV)

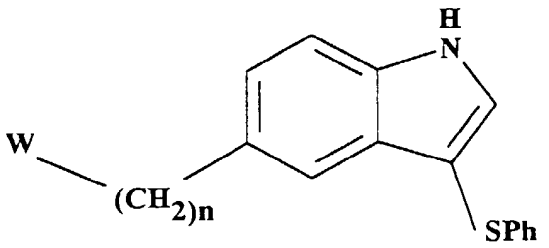


(XXXX)

wherein n and W are as hereinbefore defined, typically by refluxing in an aprotic solvent, such as chloroform, in the presence of polyphosphate ester.

Compounds of formula (XXXV) may be prepared by reacting a compound of formula (II) wherein n and W are as hereinbefore defined with 3-cyanopropanal, or a carbonyl-protected form thereof, such as the diethyl acetal, typically in an aqueous acid, for example, dil. HCl.

Compounds of formula (XXXI) may be prepared by reducing a compound of formula (XXXII)



(XXXII)

wherein n and W are as hereinbefore defined, typically by heating with Raney nickel in a polar solvent, such as IPA.

Compounds of formula (XXXII) may be prepared by reacting a hydrazine of formula (II) wherein n and W are as hereinbefore defined with phenylthioacetaldehyde, or a carbonyl-protected form thereof, for example, the diethyl acetal, in a polar solvent, such as acidified ethanol.

For a better understanding of the invention, the following Examples are given by way of illustration.

SYNTHETIC EXAMPLES

Synthetic Example 1

Preparation of (S)-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl]ethylamine

(a) (S)-Methyl 4-nitrophenylalanate hydrochloride

Methanol (110ml) was treated dropwise with thionyl chloride (26.3g) at -10° C and L-4-nitrophenylalanine (Fluka, 21.7g) added to the resulting solution as a solid. The mixture was stirred overnight at room temperature and the methanol removed in vacuo to give the desired product as a pale yellow solid (21.2g).

(b) (S)-2-Amino-3-(4-nitrophenyl)propanol

The product from step (a) (21.2g) was dissolved in ethanol/water (190ml, 100/90 v/v) and the solution added dropwise at 0°C to a stirred solution of sodium borohydride (13.0g) in ethanol/water (190ml, 100/90 v/v). The resulting mixture was refluxed for 2.5 hours, cooled and the precipitate filtered off. The ethanol was partially removed from the filtrate in vacuo and the resulting precipitate filtered off and dried to give the desired product as a pale yellow solid (7.5g).

(c) (S)-4-(4-Nitrobenzyl)-1,3-oxazolidin-2-one

The product from step (b) (4.9g) was suspended in toluene, the suspension cooled to 0°C and a solution of potassium hydroxide (7.0g) in water (56ml) added dropwise. A solution of phosgene (62.5ml of a 12% w/v solution in toluene) was added dropwise to the resulting solution over 30 minutes and stirring continued for 1 hour. The mixture was extracted with ethyl acetate and the extracts washed with brine, dried and evaporated in vacuo to give a yellow oil. Crystallisation from ethyl acetate gave the desired product as pale yellow crystals (2.3g).

(d) (S)-4-(4-Aminobenzyl)-1,3-oxazolidin-2-one hydrochloride

A suspension of the product from step (c) (0.79g) and 10% palladium on carbon (0.26g) in a mixture of ethanol (15ml), water (11ml), ethyl acetate (2.0ml) and aqu. 2N HCl (2.3ml) was stirred under 1 atmos. pressure of hydrogen until uptake ceased. The mixture was filtered through Hyflo and the filtrate evaporated in vacuo to give the desired product as a pale yellow foam (0.79g).

(e) (S)-4-(4-Hydrazinobenzyl)-1,3-oxazolidin-2-one hydrochloride

The product from step (d) (0.79g) was suspended in water (4.8ml) and c.HCl (8.1ml) added dropwise. The resulting mixture was cooled to -5°C and a solution of sodium nitrite (0.24g) in water (2.4ml) added dropwise to the stirred mixture over 15 minutes followed by 30 minutes' stirring at -5 to 0°C. The solution was then added at 0° C over 15 minutes to a stirred solution of tin (II) chloride (3.8g) in c.HCl (6.9ml), followed by 3 hours' stirring at room temperature. The solution was evaporated in vacuo and the residue triturated with ether to give the desired product as a pale yellow solid (0.96g).

(f) (S)-2-[5-(2-Oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl]ethyl-amine

The product from step (e) (0.84g) was dissolved in ethanol/water (125ml, 5:1) and the solution treated with 4-chlorobutanal dimethylacetal (JACS 1365 (1951), 0.52g). The mixture was refluxed for 2 hours, the solvent removed in vacuo and the residue eluted through a silica column using DCM/EtOH/NH_4OH(30:8:1) as eluant. The desired product was obtained as a colourless oil (0.21g).

Salt of Synthetic Example 1

Maleate

Ethanolic maleic acid (1.0 equiv.) was added dropwise to the free base (0.21g) and the ethanol evaporated in vacuo. The resulting gum was freeze-dried from water to give the desired product as a white lyopholate (0.22g), $[a]_D^{21}$ -5.92° (c = 0.3, MeOH).
^{1}H NMR (DMSO-d_6, δ): 2.7-3.5 (6H, m, CH_2), 3.35 (2H, s, NH_2), 4.05 (2H, m, CH_2), 4.25 (1H, m, CH), 6.05 (2H, s, maleic acid), 6.98 (1H, d, Ar), 7.2 (1H, s, Ar), 7.3 (1H, d, Ar), 7.4 (1H, s, Ar), 7.75 (1H, s, NH) and 10.9 (1H, s, NH)
Microanalysis: C 55.03 (54.96), H 5.54 (5.85), N 10.30 (10.68)

Synthetic Example 2

Preparation of (S)-N,N-dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl]ethylamine 0.9 isopropanolate 0.5 hydrate

A solution of formaldehyde (0.03g) in methanol (1.8ml) was added to a solution of the free base from step (f) of Synthetic Example 1 (0.12g) and sodium cyanoborohydride (0.04g) in a mixture of methanol (5.5ml) and glac. acetic acid (0.14g) and the resulting mixture stirred overnight at room temperature. The pH was adjusted to 8.0 using aqu. K_2CO_3 and the mixture extracted with ethyl acetate. The combined extracts were washed with brine, dried and evaporated to give a colourless oil (0.14g) which crystallised from isopropanol to give the desired product as a white crystalline solid (0.10g), mp 139-141°C.
^{1}H NMR (DMSO-d_6, δ): 2.2 (6H, s, NMe_2), 2.5 (2H, m, CH_2Ar), 2.7-3.0 (4H, m, CH_2), 4.1 (2H, m, CH_2O), 4.3 (1H, m, CH), 6.9 (1H, d, Ar), 7.1 (1H, s, Ar), 7.3 (1H, d, Ar), 7.4 (1H, s, Ar), 7.7 (1H, s, NHCO) and 10.7 (1H, s, NH).
Microanalysis: C 64.26 (64.11), H 8.28 (8.34), N 12.02 (12.00) $[\alpha]_D^{22}$ -5.79° (c = 0,5, MeOH)

Salts of Synthetic Example 2

Maleate

A solution of maleic acid (0.17g) in ethanol (5ml) was added to a solution of the free base (0.5g) in ethanol (5ml). The mixture was evaporated in vacuo and the resulting oil triturated with ether and methanol to give the maleate salt as a white solid which was recrystallised from ethanol (0.45g), mp 151-152° C.

Hydrochloride

Ethereal HCl (1.1 equivs.) was added dropwise to a stirred solution of the free base (0.35g) in methanol (1ml) at 0°C. The hydrochloride salt precipitated as an oil. The mixture was evaporated in vacuo and the resulting foam crystallised from isopropanol to give the desired product as a white solid (0.36g), mp 118-120°C, $[\alpha]_D^{23}$ -9.35 (c = 0.31, water).

Succinate

A solution of succinic acid (0.36g) in ethanol (10ml) was added to a solution of the free base (1.0g) in ethanol (10ml). The mixture was evaporated in vacuo and the resulting foam triturated with isopropanol to give the succinate salt as a white solid (1.0g), mp 122-123°C.

Benzoate

A solution of benzoic acid (0.37g) in ethanol (10ml) was added to a solution of the free base (1.0g) in ethanol (10ml). The mixture was evaporated in vacuo and the resulting foam crystallised from ethyl acetate to give the benzoate salt as a white solid (0.74g), mp 90-92°C.

Synthetic Example 3

Alternative preparation of (S)-N,N-dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-yl-methyl)-1H-indol-3-yl]ethylamine 0.9 isopropanolate 0.5 hydrate

4-Dimethylaminobutanal diethylacetal (Croatica Chemica Acta 36, 103 (1964), 3.9g) was added to a solution of the product from step (e) of Synthetic Example 1 (10.4g) in a mixture of acetic acid (50ml) and water (150ml) and the resulting mixture refluxed for 4.5 hours. The mixture was cooled, evaporated in vacuo and the residue eluted through a silica column using DCM/EtOH/NH_4OH (50:8:1) as eluant to give the desired product as a pale yellow oil which crystallised from isopropanol as a white crystalline solid (3.5g), mp 138-140°C. ^1H NMR, microanalysis and $[\alpha]_D$ as for product of Synthetic Example 2.

Synthetic Example 4

Preparation of (±)-3-(1-methyl-4-piperidyl)-5-(2-oxo-1,3-oxazolidin-4-yl-methyl)-1H-indole

(a) 3-(1-Methyl-1,2,3,6-tetrahydro-4-pyridyl)-1H-indole-5-carbo-nitrile

5-Cyanoindole (Aldrich, 20.0g) was added to a solution of KOH (22.4g) in methanol (200ml). N-Methyl-4-piperidone (Aldrich, 40.4g) was then added dropwise and the resulting mixture refluxed for 4 hours, then cooled and poured into water. The resulting precipitate was filtered off and dried to give the desired product as a pale pink crystalline solid (32.6g).

(b) 3-(1-Methyl-1,2,3,6-tetrahydro-4-pyridyl)-1H-indole-5-carbaldehyde

Raney nickel (ca 10g) was added to a solution of the product from step (a) (5.0g) and sodium hypophosphite (6.0g) in a mixture of water (25ml), glac. acetic acid (25ml) and pyridine (50ml) at 45°C. The resulting mixture was stirred at 45°C for 1 hour, cooled and basified to pH 9 with 0.88 NH_4OH. The mixture was filtered through Hyflo and the filtrate extracted with chloroform. The combined extracts were dried and evaporated in vacuo to give the desired product as an off-white solid which was recrystallised from ethanol (2.4g).

(c) 5-[3-(1-Methyl-1,2,3,6-tetrahydro-4-pyridyl)-1H-indol-5 ylmethylene]-2,4-imidazolidinedione

A mixture of the product from step (b) (2.4g), hydantoin (Aldrich, 0.98g) and ammonium acetate (0.74g) in glac. acetic acid (2.4ml) was heated at 120°C for 4 hours. The mixture was cooled and the resulting precipitate filtered off and dried to give the desired product as a yellow solid (2.4g).

(d) (±)-5-(2,5-Dioxo-4-imidazolidinylmethyl)-3-(1-methyl-4-piperidyl)-1H-indole

The product from step (c) (2.4g) was suspended in a mixture of water (100ml) and ethanol (200ml) and 10% w/w Pd/C (0.25g) added. The mixture was stirred under 1 atmos. pressure of hydrogen for 17 hours when uptake was complete. The mixture was filtered through Hyflo and the filtrate evaporated in vacuo to give the desired product as a colourless solid (2.4g).

(e) (±)-3-[3-(1-Methyl-4-piperidyl)-1H-indol-5-yl]alanine

A solution of the product from step (d) (2.4g) and barium hydroxide hydrate (8.4g) in water (50ml) was refluxed for 72 hours, then cooled and evaporated in vacuo. The residue was taken up in hot methanol and filtered to remove barium salts. The filtrate was evaporated in vacuo, the residue dissolved in water and dry ice added to precipitate barium carbonate. The latter was filtered off and the filtrate evaporated in vacuo to give the desired product as a yellow foam (1.3g).

(f) (±)-Methyl 3-[3-(1-methyl-4-piperidyl)-1H-indol-5-yl]alanate

A solution of the product from step (e) (6.2g) in methanol (40ml) was added dropwise to a solution of thionyl chloride (2.9ml) in methanol (35ml) at -10°C. The resulting mixture was stirred overnight at room temperature, then evaporated in vacuo and the residue eluted through a silica column using DCM/EtOH/NH_4OH (30:8:1) as eluant. The eluate was evaporated in vacuo to give the desired product as a yellow foam (4.8g).

(g) (±)-3-[3-(1-Methyl-4-piperidyl)-1H-indol-5-yl]-2-amino-1-propanol

A solution of the product from step (f) (4.8g) in water (20ml) and ethanol (20ml) was added dropwise to a suspension of sodium borohydride (0.61g) in a mixture of water (20ml) and ethanol (20ml) at 0°C. The resulting mixture was refluxed for 3 hours, then evaporated in vacuo and the residue eluted through a silica column using DCM/EtOH/NH_4OH (30:8:1) as eluant. The eluate was evaporated in vacuo to give the desired product as a colourless foam (1.6g).

(h) (±)-3-(1-Methyl-4-piperidyl)-5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indole

A mixture of the product from step (g) (1.6g), diethyl carbonate (0.73ml) and potassium carbonate (0.08g) was heated at 130°C for 5 hours. The mixture was cooled, taken up in methanol and the insoluble potassium carbonate filtered off. The filtrate was evaporated in vacuo and the residue eluted through a silica colum using DCM/EtOH/NH_4OH (30:8:1) as eluant. The eluate was evaporated in vacuo and the residue recrystallised from isopropanol/ether to give the desired product as a colourless crystalline solid (1.1g), mp 191-192°C.
^{1}H NMR (DMSO-d_6, δ): 1.6-1.8 (2H, 2 x CHNMe), 1.8-2.1 (4H, 2 x CH_2), 2.2 (3H, s, NMe), 2.6-3.0 (2H, 2 x CHNMe; 1H, CH; 2H, CH_2Ar), 3.9-4.1 (2H, m, CH_2O), 4.2-4.4 (1H, m, CHN), 6.9 (1H, d, Ar), 7.1 (1H, d, Ar), 7.3 (1H, d, Ar), 7.4 (1H, s, Ar), 7.8 (1H, s, NHCO) and 10.7 (1H, s, NH)

Salt of Synthetic Example 4

Hydrochloride

c.HCl (1.0 equiv.) was added dropwise to a stirred solution of the free base (1.1g) in ethanol (5ml) at 5°C. The addition of ether to the resulting mixture precipitated the desired product as a white solid (1.1g), mp 235-236°C (dec).

Synthetic Example 5

Preparation of (R)-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl]ethylamine

(a) (R)-4-(4-nitrobenzyl)-1,3-oxazolidin-2-one

A solution of D-4-nitrophenylalanine (Fluka, 53g) in dimethoxyethane (250ml) was warmed to 67°C and $BF_3.Et_2O$ (Aldrich, 37ml) added over 1 hour. The resulting solution was stirred at 67°C for 1 hour, then heated to 80°C and $BH_3.Me_2S$ (Aldrich, 40ml) added over 1 hour at 80-85°C. The resulting solution was heated at 85° C for 4 hours, then cooled and methanol (40ml) added. The solution was heated to 85°C and the solvents removed by distillation to 1/3 of the original bulk. 6N aqu. NaOH (136ml) was added to the hot solution which was then heated at 85°C for 1/2 hour, cooled and DCM (100ml) added. The solution was cooled to -15 to -20°C and a solution of trichloromethyl chloroformate (Aldrich, 18.2ml) in DCM (23ml) added at below -10°C. The pH was maintained at 9-11 by periodic additions of 6N aqu. NaOH. The resulting solution was stirred at room temperature for 1 hour, then diluted with water and extracted with DCM. The combined extracts were washed with water and brine, dried and evaporated in vacuo to give the desired product as a pale brown solid which was recrystallised from ethyl acetate to give a pale yellow solid (35g), mp 113-115°, $[\alpha]_D^{21}$ +46.47° (c = 0.56, MeOH).

(b) ((R)4-(4-Aminobenzyl)-1,3-oxazolidin-2-one hydrochloride

The product from step (a) (10.0g) was suspended in a mixture of water (120ml), ethanol (60ml) and 2N aqu. HCl (22.5ml) and 10% w/w Pd/C (1.0g) added. The mixture was stirred under 1 atmos. pressure of hydrogen for 8 hours when uptake was complete. The mixture was filtered through Hyflo and the filtrate evaporated in vacuo to give the desired product as a colourless glass (10.3g).

(c) (R)-4-(4-Hydrazinobenzyl)-1,3-oxazolidin-2-one hydrochloride

The product from step (b) (10.3g) was suspended in water (53ml) and c.HCl (106ml) added dropwise. The resulting mixture was cooled to -5°C and a solution of sodium nitrite (3.2g) in water (30ml) added dropwise to the stirred mixture over 15 minutes followed by 30 minutes' stirring at -5 to 0°C. The solution was then added at 0° C over 15 minutes to a stirred solution of tin (II) chloride (51g) in c.HCl (91ml), followed by 3 hours' stirring at room temperature. The solution was evaporated in vacuo and the residue triturated with ether to give the desired product as a pale yellow solid (11g).

(d) (R)-2-[5-(2-Oxa-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl]-ethylamine

The product from step (c) (8.8g) was dissolved in ethanol/water (500ml, 5:1 v/v) and the solution treated with 4-chlorobutanal dimethylacetal (J.Amer.Chem.Soc. 1365 (1951), 5.5g). The mixture was refluxed for 2 hours, the solvent removed in vacuo and the residue eluted through a silica column using DCM/EtOH/NH_4OH (30:8:1 v/v/v) as eluant. The desired product was obtained as a pale yellow oil (0.60g).

Salt of Synthetic Example 6

Hydrochloride

c.HCl (0.06ml) was added dropwise to a stirred solution of the free base (0.16g) in ethanol (2ml) at 0°C. The hydrochloride o salt was precipitated as a fawn solid, mp 269-271°C, $[\alpha)_D^{21}$ +5.88° (c = 0.27, MeOH).

Synthetic Example 6

Preparation of (R)-N,N-dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-yl-methyl)-1H-indol-3-yl]ethylamine

A solution of 35% w/v aqu. formaldehyde (0.3ml) in methanol (2.0ml) was added to a solution ofthe product from step (d) of Synthetic Example 6 (0.44g) and sodium cyanoborohydride (0.13g) in a mixture of methanol (8.5ml) and glac. acetic acid (0.51g) at 10°C and the resulting mixture stirred at room temperature for 2.5 hours. 2N aqu. NaOH (1.3ml) was added, then sodium borohydride (0.19g) followed by 2N aqu. HCl (1.3ml). The methanol was evaporated in vacuo and the remaining solution diluted with water, taken to pH 7 with solid potassium carbonate and washed with ethyl acetate. Further potassium carbonate was added to pH 11 and the solution extracted with ethyl acetate. The combined extracts were evaporated in vacuo to give the desired product as a white foam (0.45g).

Salt of Synthetic Example 6

Hydrochloride

c.HCl (0.16ml) was added dropwise to a stirred solution of the free base (0.45g) in ethanol (4.5ml) at 0°C. The mixture was evaporated in vacuo and the resulting foam triturated with ethyl acetate to give the desired product as a white solid, mp 130°C, $[\alpha]_D^{21}$ +5.15° (c = 0.77, MeOH).

Synthetic Example 7

Preparation of (S)-N,N-dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl]ethylamine

(a) (S)-5-(4-Nitrobenzyl)-1,3-imidazolidin-2,4-dione

Benzyl isocyanate (Aldrich, 3.2g) was added to a solution of L-4-nitrophenylalanine (Aldrich, 4.2g) and potassium hydroxide (1.3g) in water (40ml) at 0°C. The mixture was heated at 60-70°C for 2 hours, filtered and the filtrate acidified with c.HCl to give and off-white solid which was filtered off, suspended in 2N aqu. HCl (20ml) and refluxed for 2 hours.

The cooled mixture was diluted with water and filtered to give the desired product as a white solid (5.6g).

(b) (S)-N,N-Dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl]ethylamine

By steps identical to steps (d) to (f) of Synthetic Example 1 and Synthetic Example 2 or steps (d) and (e) of Synthetic Example 1 and Synthetic Example 3 and steps (e) to (h) of Synthetic Example 4, the product from step (a) was converted to (S)-N,N-dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl]ethylamine.

Synthetic Example 8

Preparation of (S)-N,N-dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl]ethylamine

(a) (S)-4-(4-Hydrazinobenzyl)-1,3-oxazolidin-2-one hydrochloride

By steps analogous to steps (a) to (c) of Synthetic Example 6, L-4-nitrophenylalanine was converted to (S)-4-(4-hydrazinobenzyl)-1,3-oxazolidin-2-one hydrochloride

(b) (S)-4-{4-[2-(3-cyanopropylidene)hydrazino]benzyl}-1,3-oxazolidin-2-one

1M aqu. HCl (4.0ml) was added to a solution of the product from step (a) (2.4g) in water (35ml). 3-Cyanopropanal diethylacetal (Aldrich, 1.7g) was added at room temperature and the mixture stirred for 2 hours. Further acetal (0.20g) was added and the mixture stirred for another 20 minutes. The aqueous phase was decanted from the resulting gum and extracted with ethyl acetate. The extracts were combined with the gum and evaporated in vacuo to give the desired product (2.5g).

(c) (S)-3-Cyanomethyl-5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indole

A solution of the product from step (b) (2.5g) and polyphosphate ester (20.0g) in chloroform (40ml) was refluxed for 20 minutes. Ice was added to the cooled mixture and the chloroform evaporated in vacuo. The remaining aqueous phase was extracted with ethyl acetate and the combined extracts evaporated in vacuo to give the desired product as a pale yellow oil (1.8g).

(d) (S)-N,N-Dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl]ethylamine

A suspension of the product from step (c) (1.3g) and 10% w/w Pd/C (1.0g) in 30% w/w ethanolic dimethylamine (25ml) was hydrogenated for 24 hours and filtered through Hyflo. Fresh Pd/C (0.7g) and ethanolic dimethylamine (5ml) were added to the filtrate and hydrogenation continued for a further 16 hours. The mixture was filtered through a silica column using DCM/EtOH/NH_4OH (40:8:1) as eluant to give the desired product as a colourless foam (0.3g). Elemental analysis and ^1H NMR were consistent with the proposed structure.

PHARMACEUTICAL FORMULATION EXAMPLES

In the following Examples, the "active ingredient" may be any compound of the invention and/or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof.

(1) Tablet formulations

(i) Oral

	Mg/tablet		
	A	B	C

Active ingredient	25	25	25
Avicel	13	-	7
Lactose	78	47	-
Starch (maize)	-	9	-
Starch (pregelatinised, NFI5)	-	-	32
Sodium starch glycollate	5	-	-
Povidone	3	3	
-			
Magnesium stearate	1	1	1
	125	85	65

(ii) Sublingual

	Mg/tablet	
	D	E
Active ingredient	25	25
Avicel	10	-
Lactose	-	36
Mannitol	51	57
Sucrose	-	3
Acacia	-	3
Povidone	3	-
Magnesium stearate	1	1
	90	125

Formulations A to E may be prepared by wet granulation of the first six ingredients with the povidone, followed by addition of the magnesium stearate and compression.

(iii) Buccal

	Mg/tablet
Active ingredient	25
Hydroxypropylmeth	

cellulose (HPMC)	25
Polycarbophil	39
Magnesium stearate	1
	90

The formulation may be prepared by direct compression of the admixed ingredients.

(2) Capsule formulations

(i) Powder

	Mg/capsule	
	F	G
Active ingredient	25	25
Avicel	45	-
Lactose	153	-
Starch (1500 NF)	-	117
Sodium starch glycollate	-	6
Magnesium stearate	2	2
	225	150

Formulations F and G may be prepared by admixing the ingredients and filling two-part hard gelatin capsules with the resulting mixture.

(ii) Liquid fill

	Mg/capsule	
	H	I
Active ingredient	25	25
Macrogol 4000 BP	200	-
Lecithin	-	100
Arachis oil	-	100
	225	225

Formulation H may be prepared by melting the Macrogol 4000 BP, dispersing the active ingredient in the melt and filling two-part hard gelatin capsules therewith. Formulation I may be prepared by dispersing the active ingredient in the lecithin and arachis oil and filling soft, elastic gelatin capsules with the dispersion.

(iii) Controlled release

	Mg/capsule
Active ingredient	25
Avicel	123
Lactose	62
Triethylcitrate	3
Ethyl cellulose	12
	225

The formulation may be prepared by mixing and extruding the first four ingredients and spheronising and drying the extrudate. The dried pellets are coated with ethyl cellulose as a release controlling membrane and filled into two-part, hard gelatin capsules.

(3) Intravenous injection formulation

	% by weight
Active ingredient	2%
Hydrochloric acid) Citrate buffer)	q.s. to pH 7
Water for Injections	to 100%

The active ingredient is taken up in the citrate buffer and sufficient hydrochloric acid added to affect solution and adjust the pH to 7. The resulting solution is made up to volume and filtered through a micropore filter into sterile glass vials which are sealed and oversealed.

(4) Intranasal formulation

	% by weight
Active ingredient	0.5%
Hydrochloric acid) Citrate buffer)	q.s. to pH 7
Methyl hydroxybenzoate	0.2%
Propyl hydroxybenzoate	0.02%
Water for Injections to	100%

The active ingredient is taken up in a mixture of the hydroxybenzoates and citrate buffer and sufficient hydrochloric acid added to affect solution and adjust the pH to 7. The resulting solution is made up to volume and filtered through a micropore filter into sterile glass vials which are sealed and oversealed.

(5) Intramuscular injection formulation

Active ingredient	0.05 g

(continued)

Benzyl alcohol		0.10 g
Glycofurol 75		1.45 g
Water for Injections to	q.s.	3.00 ml

The active ingredient is dissolved in the glycofurol. The benzyl alcohol is added and dissolved and water added to 3 ml. The mixture is filtered through a micropore filter into sterile glass vials which are sealed and oversealed.

(6) Syrup formulation

Active ingredient		0.05 g
Sorbitol solution		1.50 g
Glycerol		1.00 g
Sodium benzoate		0.005 g
Flavour		0.0125 ml
Purified water to	q.s.	5.0 ml

The sodium benzoate is dissolved in a portion of the purified water and the sorbitol solution added. The active ingredient is added and dissolved. The resulting solution is mixed with the glycerol and made up to the required volume with purified water.

(7) Suppository formulation

	Mg/suppository
Active ingredient (63lm)*	50
Hard Fat, BP (Witepsol H15 - Dynamit NoBel)	1950
	2000

* The active ingredient is used as a powder wherein at least 90% of the particles are of 63lm diameter or less.

One-fifth of the Witepsol H15 is melted in a steam-jacketed pan at 45° C maximum. The active ingredient is sifted through a 2001m sieve and mixed with the molten base using a Silverson mixer fitted with a cutting head until a smooth dispersion is achieved. Maintaining the mixture at 45°C, the remaining Witepsol H15 is added to the suspension which is stirred to ensure a homogenous mix. The entire suspension is then passed through a 250lm stainless steel screen and, with continuous stirring, allowed to cool to 40°C. At a temperature of 38-40°C, 2.0g aliquots of the mixture are filled into suitable plastic moulds and the suppositories allowed to cool to room temperature.

(8) Pessary formulation

	Mg/pessary
Active ingredient (63lm)	50
Anhydrous dextrose	470
Potato starch	473
Magnesium stearate	473
	1000

The above ingredients are mixed directly and pessaries prepared by compression of the resulting mixture.

BIOLOGICAL ASSAY

The compounds prepared in Synthetic Examples 2/3 were tested for their activity as agonists for the "5-HT_1-like" receptor mediating smooth muscle contraction by the following method.

Right and left lateral saphenous veins were obtained from male New Zealand White rabbits (2.4-2.7 kg) which had been killed by intravenous injection of pentobarbitone sodium (60 mg/kg). Ring segments (3-5 mm wide) prepared from each vessel were suspended between two wire hooks and immersed in 20 ml organ baths containing Krebs' solution (pH 7.4) of the following composition (mM): NaCl 118.41, $NaHCO_3$ 25.00, KCl 4.75, KH_2PO_4 1.19, $MgSO_4$ 1.19, glucose 11.10 and $CaCl_2$ 2.50. Cocaine (301M) was present in the Krebs' solution throughout the experiment to prevent the uptake of amines by sympathetic neurones. The Krebs' solution was maintained at 37°C and continually gassed with 95% oxygen/5% carbon dioxide. Increases in tissue isometric force were measured using Grass FT03C force displacement transducers and recorded on a Gould BD-212 pen recorder.

A force of 1.0g was applied to each preparation and re-established twice during a subsequent period of 30 minutes. During this period, tissues were exposed to pargyline (500IM) to irreversibly inhibit monoamine oxidase and to phenoxybenzamine (0.1IM) to inactivate a_1-adrenoceptors. At the end of the 30 minutes, the inhibitors were removed by several changes of the organ bath Krebs' solution.

Agonist activity was assessed by cumulative additions of the test compound, its concentration being increased in 0.5 $\log_{10}$ unit increments until further additions caused no further change in tissue force. In each experiment, the activity of the test compound was compared to the activity of 5-HT. Activity was expressed in terms of the $p[A_{50}]$($-\log_{10}$[M], where M is the molar concentration of agonist required to produce half the maximum effect). The results obtained for the compounds of Synthetic Examples 2/3 are shown in Table 1.

Table 1

Example	Activity $p[A_{50}]$
2/3	7.0

TOXICITY DATA

The hydrochloride salt of the compound of Synthetic Examples 2/3 was administered orally by gavage to Wistar rats as a solution in distilled water at dosages of 25, 100 and 200mg/kg base and to Beagle dogs at dosages of 0.25, 0.50, 1.0 and 2.0mg/kg base once a day for 14 days. In a separate dog study over 30 days, the dosage of the free base was increased from 2mg/kg on Day 1 to 100mg/kg on Day 30. The free base was also administered orally to cynomolgus monkeys at a dosage of 50mg/kg once a day for 15 days.

No evidence of toxicity was observed in any of the aforementioned studies at any of the dosages used.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. The compound N,N-dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl]ethylamine in either its (S) or (R) form or as a mixture thereof in any proportions, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof.

2. The compound of formula (I) as claimed in Claim 1, which is (S)-N,N-dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl]ethylamine, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof.

3. A compound as claimed in Claim 1 or Claim 2, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof for use as a therapeutic agent.

4. A compound as claimed in Claim 1 or Claim 2, or a physiologically acceptable salt, solvate or physiologically functional derivative thereof, for use in the prophylaxis or treatment of a clinical condition for which a "5-HT_1-like" receptor agonist is indicated.

5. A compound as claimed in Claim 1 or Claim 2, or a physiologically acceptable salt, solvate, or physiologically

functional derivative thereof, for use in the prophylaxis or treatment of migraine.

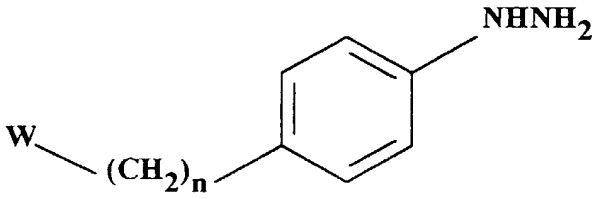
6. Use of a compound as claimed in Claim 1 or Claim 2, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof, in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a "5-HT_1-like" receptor agonist is indicated.

7. Use of a compound as claimed in Claim 1 or Claim 2, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of migraine.

8. A medicament comprising a compound as claimed in Claim1 or Claim 2 or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof, a pharmaceutically acceptable carrier and, optionally, one or more other physiologically active agents.

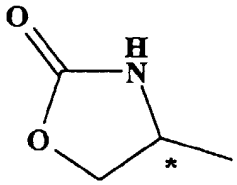
9. A medicament as claimed in Claim 8 which is in the form of a tablet or capsule.

10. A process for the preparation of the compound N,N-dimethyl-2-[5-2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl] ethylamine in either its (S) or (R) form or as a mixture thereof in any proportions;
which comprises reacting a compound of formula (II)

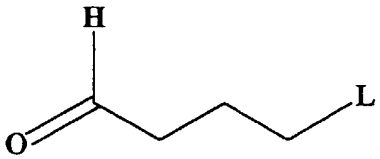


(II)

wherein n is 1 and W is a group



and the chiral centre * is in its (S) or (R) form or is a mixture thereof in any proportions with a compound of formula (III)



(III)

or a carbonyl-protected form thereof, wherein L is a suitable leaving group or protected aminol group which may be converted in situ to a dimethyl amino group or is -NR^1R^2 wherein R^1 and R^2 are each methyl.

11. A method of preparing a medicament which comprises

a) preparing the compound N,N-dimethyl-2-[5-(2-oxa-1,3-oxazolidin-4-yl methyl)-1H-indol-3-yl]ethylamine in either its (S) or (R) form or as a mixture thereof in any proportions, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof by a process as claimed in Claim 10; and

b) admixing the product from step a) with a pharmaceutically acceptable carrier and, optionally, one or more other physiologically active agents.

12. A method as claimed in Claim 11 which comprises an additional step c) wherein the admixture from step b) is formed into a tablet or capsule.

Claims for the following Contracting States : ES, GR

1. A Process for the manufacture of a pharmaceutical formulation comprising at least the compound

N,N-dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl]ethylamine

in either its (S) or (R) form or as a mixture thereof in any proportions, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof, which process comprises the step of admixing said compound with one or more pharmaceutically acceptable excipients, carriers and/or diluents.

2. A Process as claimed in Claim 1, wherein said compound is (S)-N,N-dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl]ethylamine or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof.

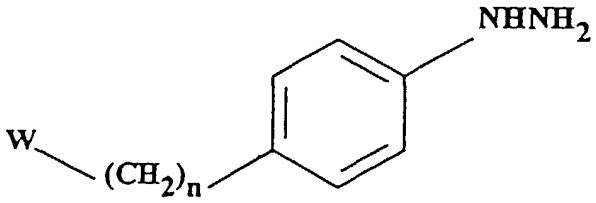
3. A Process as claimed in Claim 1 or Claim 2, wherein said pharmaceutical formulation is for use in the prophylaxis or treatment of a clinical condition for which a "5-HT_1-like" receptor agonist is indicated.

4. A Process as claimed in Claim 1 or Claim 2, wherein said pharmaceutical formulation is for use in the prophylaxis or treatment of migraine.

5. Use of a compound as defined in Claim 1 or Claim 2, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof, in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a "5-HT_1-like" receptor agonist is indicated.

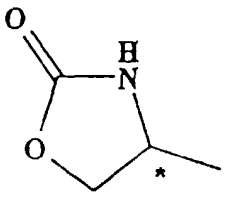
6. Use of a compound as defined in Claim 1 or Claim 2, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof, in the manufacture of a medicament for the prophylaxis or treatment of migraine.

7. A process for the preparation of the compound N,N-dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl] ethylamine in either its (S) or (R) form or as a mixture thereof in any proportions.
which comprises reacting a compound of formula (II)



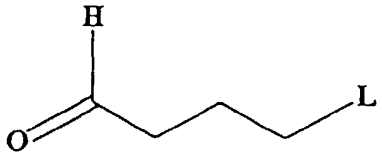
(II)

wherein n is 1 and W is a group



and the chiral centre * is in its (S) or (R) form or is a mixture thereof in any proportions with a compound of formula

(III)



(III)

or a carbonyl-protected form thereof, wherein L is a suitable leaving group or protected aminol group which may be converted in situ to a dimethyl amino group or is -NR^1R^2 wherein R^1 and R^2 are each methyl.

8. A method of preparing a medicament which comprises

a) preparing the compound N,N-dimethyl-2-[5-(2-oxa-1,3-oxazolidin-4-yl methyl)-1H-indol-3-yl]ethylamine in either its (S) or (R) form or as a mixture thereof in any proportions, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof by a process as claimed in Claim 7; and

b) admixing the product from step a) with a pharmaceutically acceptable carrier and, optionally, one or more other physiologically active agents.

9. A method as claimed in Claim 8 which comprises an additional step c) wherein the admixture from step b) is formed into a tablet or capsule.

10. The compound N,N-dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl]ethylamine in either its (S) or (R) form or as a mixture thereof in any proportions, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof.

11. The compound of formula (I) as claimed in Claim 10, which is (S)-N,N-dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl]ethylamine or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof.

12. A compound as claimed in Claim 10 or Claim 11, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof for use as a therapeutic agent.

13. A compound as claimed in Claim 10 or Claim 11, or a physiologically acceptable salt, solvate or physiologically functional derivative thereof for use in the prophylaxis or treatment of a clinical condition for which a "5-HT_1-like" receptor agonist is indicated.

14. A compound as claimed in Claim 10 or Claim 11, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof, for use in the prophylaxis or treatment of migraine.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT LI, LU, NL, SE

1. N,N-Dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl]ethylamin in seiner (S)- oder (R)-Form oder in Form eines Gemisches daraus in beliebigen Verhältnissen, oder ein physiologisch akzeptables Salz, Solvat oder physiologisch funktionelles Derivat davon.

2. Verbindung der Formel (I) nach Anspruch 1, nämlich (S)-N,N-Dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl]ethylamin, oder ein physiologisch akzeptables Salz, Solvat oder physiologisch funktionelles Derivat davon.

3. Verbindung nach Anspruch 1 oder 2, oder ein physiologisch akzeptables Salz, Solvat oder physiologisch funktionelles Derivat davon, zur Verwendung als therapeutisches Mittel.

4. Verbindung nach Anspruch 1 oder 2, oder ein physiologisch akzeptables Salz, Solvat oder physiologisch funktionelles Derivat davon, zur Verwendung zur Prophylaxe oder Behandlung eines klinischen Zustandes, für den ein Agonist des "5-HT_1-ähnlichen" Rezeptors angezeigt ist.

5. Verbindung nach Anspruch 1 oder 2, oder ein physiologisch akzeptables Salz, Solvat oder physiologisch funktionelles Derivat davon, zur Verwendung zur Prophylaxe oder Behandlung von Migräne.

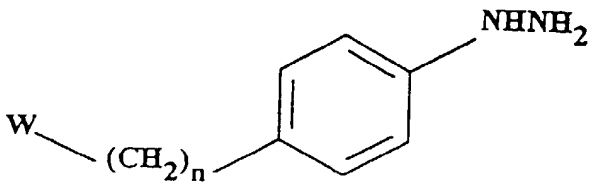
6. Verwendung einer Verbindung nach Anspruch 1 oder 2, oder eines physiologisch akzeptablen Salzes, Solvats oder physiologisch funktionellen Derivats davon, zur Herstellung eines Arzneimittels zur Prophylaxe oder Behandlung eines klinischen Zustandes, für den ein Agonist des "5-HT_1-artigen" Rezeptors angezeigt ist.

7. Verwendung einer Verbindung nach Anspruch 1 oder 2, oder eines physiologisch akzeptablen Salzes, Solvats oder physiologisch funktionellen Derivats davon, zur Herstellung eines Arzneimittels zur Prophylaxe oder Behandlung von Migräne.

8. Arzneimittel, das eine Verbindung nach Anspruch 1 oder 2, oder ein physiologisch akzeptables Salz, Solvat oder physiologisch funktionelles Derivat davon, einen pharmazeutisch akzeptablen Träger und gegebenenfalls ein oder mehrere andere physiologisch wirksame Mittel enthält.

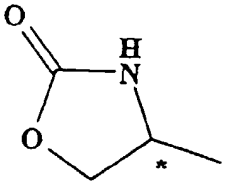
9. Arzneimittel nach Anspruch 8 in Form einer Tablette oder Kapsel.

10. Verfahren zur Herstellung der Verbindung N,N-Dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl] ethylamin in ihrer (S)- oder (R)-Form oder in Form eines Gemisches daraus in beliebigen Verhältnissen, bei dem eine Verbindung der Formel (II):

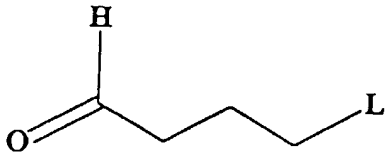


(II)

wobei n 1 und W eine Gruppe



ist und das chirale Zentrum * in seiner (S)- oder (R)-Form oder in Form eines Gemisches daraus in beliebigen Verhältnissen vorliegt, mit einer Verbindung der Formel (III):



(III)

oder einer Carbonyl-geschützten Form davon, wobei L eine geeignete Austrittsgruppe oder geschützte Amino-Gruppe, die in situ in eine Dimethylamino-Gruppe umgewandelt werden kann, oder -NR^1R^2 ist, wobei R^1 und R^2 jeweils Methyl sind, umgesetzt wird.

11. Verfahren zur Herstellung eines Arzneimittels, bei dem:

a) die Verbindung N,N-Dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl]ethylamin in ihrer (S)- oder (R)-Form oder in Form eines Gemisches daraus in beliebigen Verhältnissen, oder ein physiologisches akzeptables Salz, Solvat oder physiologisch funktionelles Derivat davon, nach einem Verfahren nach Anspruch 10 hergestellt wird, und

b) das Produkt von Schritt a) mit einem pharmazeutisch akzeptablen Träger und gegebenenfalls einem oder mehreren anderen physiologisch wirksamen Mitteln vermischt wird.

12. Verfahren nach Anspruch 11, das einen zusätzlichen Schritt c) aufweist, in dem das Gemisch aus Schritt b) zu einer Tablette oder Kapsel geformt wird.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung einer pharmazeutischen Formulierung, die zumindest die Verbindung

N,N-Dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl]ethylamin

in ihrer (S)- oder (R)-Form oder in Form eines Gemisches daraus in beliebigen Verhältnissen, oder ein physiologisch akzeptables Salz, Solvat oder physiologisch funktionelles Derivat davon, enthält, bei dem diese Verbindung mit einem oder mehreren pharmazeutisch akzeptablen Arzneimittelträgern, Trägern und/oder Verdünnungsmitteln vermischt wird.

2. Verfahren nach Anspruch 1, wobei die Verbindung (S)-N,N-Dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl]ethylamin, oder ein physiologisch akzeptables Salz, Solvat oder physiologisch funktionelles Derivat davon, ist.

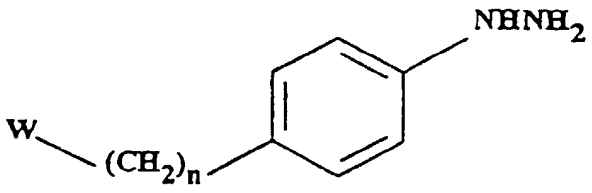
3. Verfahren nach Anspruch 1 oder 2, wobei die pharmazeutische Formulierung zur Prophylaxe oder Behandlung eines klinischen Zustandes verwendet wird, für den ein Agonist eines "5-HT_1-ähnlichen" Rezeptors angezeigt ist.

4. Verfahren nach Anspruch 1 oder 2, wobei die pharmazeutische Formulierung zur Prophylaxe oder Behandlung von Migräne verwendet wird.

5. Verwendung einer Verbindung nach Anspruch 1 oder 2, oder eines physiologisch akzeptablen Salzes, Solvats oder physiologisch funktionellen Derivats davon, zur Herstellung eines Arzneimittels zur Prophylaxe oder Behandlung eines klinischen Zustandes, für den ein Agonist eines "5-HT_1-ähnlichen" Rezeptors angezeigt ist.

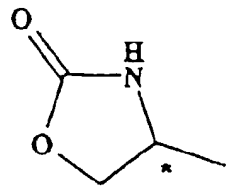
6. Verwendung einer Verbindung nach Anspruch 1 oder 2, oder eines physiologisch akzeptablen Salzes, Solvats oder physiologisches funktionellen Derivats davon, zur Herstellung eines Arzneimittels zur Prophylaxe oder Behandlung von Migräne.

7. Verfahren zur Herstellung der Verbindung N,N-Dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl] ethylamin in ihrer (S)- oder (R)-Form oder in Form eines Gemisches daraus in beliebigen Verhältnissen, bei dem eine Verbindung der Formel (II):

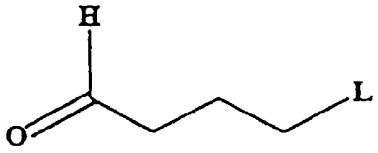


(II)

wobei n 1 und W eine Gruppe



ist und das chirale Zentrum * in seiner (S)- oder (R)-Form oder in Form eines Gemisches daraus in beliebigen Verhältnissen vorliegt, mit einer Verbindung der Formel (III):



(III)

oder einer Carbonyl-geschützten Form davon, wobei L eine geeignete Austrittsgruppe oder geschützte Amino-Gruppe, die in situ in eine Dimethylamino-Gruppe umgewandelt werden kann, oder $-NR^1R^2$ ist, wobei R^1 und R^2 jeweils Methyl sind, umgesetzt wird.

8. Verfahren zur Herstellung eines Arzneimittels, bei dem:

a) die Verbindung N,N-Dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl]ethylamin in ihrer (S)- oder (R)-Form oder in Form eines Gemisches daraus in beliebigen Verhältnissen, oder ein physiologisches akzeptables Salz, Solvat oder physiologisch funktionelles Derivat davon, nach einem Verfahren nach Anspruch 7 hergestellt wird, und

b) das Produkt von Schritt a) mit einem pharmazeutisch akzeptablen Träger und gegebenenfalls einem oder mehreren anderen physiologisch wirksamen Mitteln vermischt wird.

9. Verfahren nach Anspruch 8, das einen zusätzlichen Schritt c) aufweist, in dem das Gemisch aus Schritt b) zu einer Tablette oder Kapsel geformt wird.

10. N,N-Dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl]ethylamin in seiner (S)- oder (R)-Form oder in Form eines Gemisches daraus in beliebigen Verhältnissen, oder ein physiologisch akzeptables Salz, Solvat oder physiologisch funktionelles Derivat davon.

11. Verbindung der Formel (I) nach Anspruch 10, nämlich (S)-N,N-Dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl]ethylamin, oder ein physiologisch akzeptables Salz, Solvat oder physiologisch funktionelles Derivat davon.

12. Verbindung nach Anspruch 10 oder 11, oder ein physiologisch akzeptables Salz, Solvat oder physiologisch funktionelles Derivat davon, zur Verwendung als therapeutisches Mittel.

13. Verbindung nach Anspruch 10 oder 11, oder ein physiologisch akzeptables Salz, Solvat oder physiologisch funktionelles Derivat davon, zur Verwendung zur Prophylaxe oder Behandlung eines klinischen Zustandes, für den ein Agonist des "5-HT_1-ähnlichen" Rezeptors angezeigt ist.

14. Verbindung nach Anspruch 10 oder 11, oder ein physiologisch akzeptables Salz, Solvat oder physiologisch funktionelles Derivat davon, zur Verwendung zur Prophylaxe oder Behandlung von Migräne.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE DK, FR, GB, IT, LI, LU, NL, SE

1. Composé consistant en

   N,N-diméthyl-2-[5-(2-oxo-1,3-oxazolidine-4-ylméthyl)-1H-indole-3-yl]éthylamine
   sous sa forme (S) ou (R) ou à l'état d'un mélange de ces formes en n'importe quelles proportions, ou un de ses sels, produits de solvatation ou dérivés physiologiquement fonctionnels, physiologiquement acceptable.

2. Composé de formule (I) suivant la revendication 1, qui consiste en (S)-N,N-diméthyl-2-[5-(2-oxo-1,3-oxazolidine-4-ylméthyl)-1H-indole-3-yl]éthylamine ou un de ses sels, produits de solvatation ou dérivés physiologiquement fonctionnels, physiologiquement acceptable.

3. Composé suivant la revendication 1 ou la revendication 2, ou un de ses sels, produits de solvatation ou dérivés physiologiquement fonctionnels, physiologiquement acceptable, destiné à être utilisé comme agent thérapeutique.

4. Composé suivant la revendication 1 ou la revendication 2, ou un de ses sels, produits de solvatation ou dérivés physiologiquement fonctionnels, physiologiquement acceptable, destiné à être utilisé dans la prophylaxie ou le traitement d'un état pathologique pour lequel un agoniste des récepteurs "analogues à 5-HT_1" est indiqué.

5. Composé suivant la revendication 1 ou la revendication 2, ou un de ses sels, produits de solvatation ou dérivés physiologiquement fonctionnels, physiologiquement acceptable, destiné à être utilisé dans la prophylaxie ou le traitement de la migraine.

6. Utilisation d'un composé suivant la revendication 1 ou la revendication 2, ou d'un de ses sels, produits de solvatation ou dérivés physiologiquement fonctionnels, physiologiquement acceptable, dans la production d'un médicament destiné à la prophylaxie ou le traitement d'un état pathologique pour lequel un agoniste des récepteurs "analogues à 5-HT_1" est indiqué.

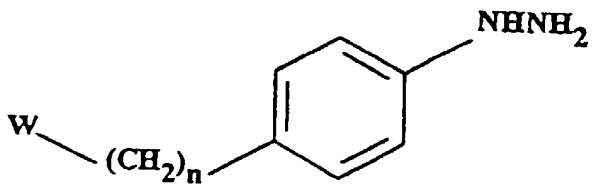
7. Utilisation d'un composé suivant la revendication 1 ou la revendication 2, ou d'un de ses sels, produits de solvatation ou dérivés physiologiquement fonctionnels, physiologiquement acceptable, dans la production d'un médicament destiné à la prophylaxie ou le traitement de la migraine.

8. Médicament comprenant un composé suivant la revendication 1 ou la revendication 2 ou un de ses sels, produits de solvatation ou dérivés physiologiquement fonctionnels, physiologiquement acceptable, un support pharmaceutiquement acceptable et, facultativement, un ou plusieurs autres agents physiologiquement actifs.

9. Médicament suivant la revendication 8, qui est sous forme d'un comprimé ou d'une capsule.

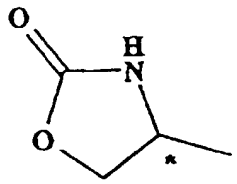
10. Procédé pour la préparation du composé consistant en

    N,N-diméthyl-2-[5-(2-oxo-1,3-oxazolidine-4-ylméthyl)-1H-indole-3-yl]éthylamine
    sous sa forme (S) ou (R) ou à l'état d'un mélange de telles formes en n'importe quelles proportions,
    qui comprend la réaction d'un composé de formule (II)

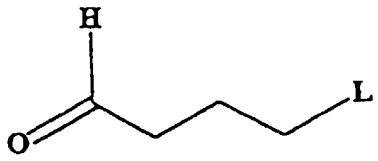


(II)

dans laquelle n est égal à 1 et W représente un groupe



et le centre chiral * est sous sa forme (S) ou (R) ou est à l'état d'un mélange de ces formes en n'importe quelles proportions, avec un composé de formule (III)



(III)

ou de ses formes à fonction carbonyle protégée, formule dans laquelle L représente un groupe partant convenable ou un groupe amino protégé qui peut être transformé in situ en un groupe diméthylamino ou représente un groupe NR^1R^2 dans lequel R^1 et R^2 représentent chacun un groupe méthyle.

11. Procédé de préparation d'un médicament, qui comprend

a) la préparation du composé consistant en N,N-diméthyl-2-[5-(2-oxa-1,3-oxazolidine-4-yl-méthyl)-1H-indole-3-yl]éthylamine sous sa forme (S) ou (R) ou à l'état d'un mélange de ces formes en n'importe quelles proportions, ou d'un de ses sels, produits de solvatation ou dérivés physiologiquement fonctionnels, physiologiquement acceptable, par un procédé suivant la revendication 10 ; et
b) le mélange du produit de l'étape a) avec un support pharmaceutiquement acceptable et, facultativement, un ou plusieurs autres agents physiologiquement acceptables.

12. Procédé suivant la revendication 11, qui comprend une étape c) supplémentaire dans laquelle le mélange de l'étape b) est mis sous forme d'un comprimé ou d'une capsule.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé pour la production d'une formulation pharmaceutique comprenant au moins le composé consistant en

N,N-diméthyl-2-[5-(2-oxo-1,3-oxazolidine-4-ylméthyl)-1H-indole-3-yl]éthylamine
sous sa forme (S) ou (R) ou à l'état d'un mélange de ces formes en n'importe quelles proportions, ou un de ses sels, produits de solvatation ou dérivés physiologiquement fonctionnels, physiologiquement acceptable, procédé qui comprend l'étape consistant à mélanger ledit composé avec un ou plusieurs excipients, supports et/ou diluants pharmaceutiquement acceptables.

2. Procédé suivant la revendication 1, dans lequel le composé consiste en (S)-N,N-diméthyl-2-[5-(2-oxo-1,3-oxazolidine-4-ylméthyl)-1H-indole-3-yl]éthylamine ou un de ses sels, produits de solvatation ou dérivés physiologiquement fonctionnels, physiologiquement acceptable.

3. Procédé suivant la revendication 1 ou la revendication 2, dans lequel la formulation pharmaceutique est destinée à être utilisée dans la prophylaxie ou le traitement d'un état pathologique pour lequel un agoniste des récepteurs "analogues à 5-HT_1" est indiqué.

4. Procédé suivant la revendication 1 ou la revendication 2, dans lequel la formulation pharmaceutique est destinée à être utilisée dans la prophylaxie ou le traitement de la migraine.

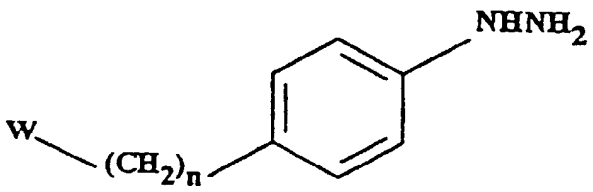
5. Utilisation d'un composé répondant à la définition suivant la revendication 1 ou la revendication 2, ou d'un de ses

sels, produits de solvatation ou dérivés physiologiquement fonctionnels, physiologiquement acceptable, dans la production d'un médicament destiné à la prophylaxie ou au traitement d'un état pathologique pour lequel un agoniste des récepteurs "analogues à 5-HT_1" est indiqué.

6. Utilisation d'un composé répondant à la définition suivant la revendication 1 ou la revendication 2, ou d'un de ses sels, produits de solvatation ou dérivés physiologiquement fonctionnels, physiologiquement acceptable, dans la production d'un médicament destiné à la prophylaxie ou au traitement de la migraine.

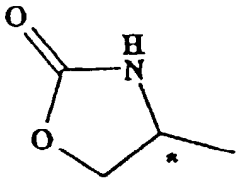
7. Procédé pour la préparation du composé consistant en

N,N-diméthyl-2-[5-(2-oxo-1,3-oxazolidine-4-ylméthyl)-1H-indole-3-yl]éthylamine
sous sa forme (S) ou (R) ou à l'état d'un mélange de ces formes en n'importe quelles proportions,
qui comprend la réaction d'un composé de formule (II)

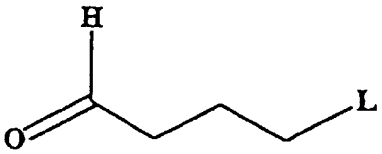


(II)

dans laquelle n est égal à 1 et W représente un groupe



et le centre chiral * est sous sa forme (S) ou (R) ou consiste en un mélange de ces formes en n'importe quelles proportions, avec un composé de formule (III)



(III)

ou d'une forme à fonction carbonyle protégée de ce composé, formule dans laquelle L représente un groupe partant convenable ou un groupe amino protégé qui peut être transformé in situ en un groupe diméthylamino ou bien représente un groupe NR^1R^2 dans lequel R^1 et R^2 représentent chacun un groupe méthyle.

8. Procédé de préparation d'un médicament, qui comprend

a) la préparation du composé consistant en N,N-diméthyl-2-[5-(2-oxa-1,3-oxazolidine-4-yl-méthyl)-1H-indole-3-yl]éthylamine sous sa forme (S) ou (R) ou à l'état d'un mélange de ces formes en n'importe quelles proportions, ou d'un de ses sels, produits de solvatation ou dérivés physiologiquement fonctionnels, physiologiquement acceptable, par un procédé suivant la revendication 7 ; et
b) le mélange du produit de l'étape a) avec un support pharmaceutiquement acceptable et, facultativement, un ou plusieurs autres agents physiologiquement actifs.

9. Procédé suivant la revendication 8, qui comprend une étape c) supplémentaire dans laquelle le mélange de l'étape b) est mis sous forme d'un comprimé ou d'une capsule.

10. Composé consistant en

N,N-diméthyl-2-[5-(2-oxo-1,3-oxazolidine-4-ylméthyl)-1H-indole-3-yl]éthylamine
sous sa forme (S) ou (R) ou à l'état d'un mélange de ces formes en n'importe quelles proportions, ou un de ses sels, produits de solvatation ou dérivés physiologiquement fonctionnels, physiologiquement acceptable.

11. Composé de formule (I) suivant la revendication 10, qui consiste en (S)-N,N-diméthyl-2-[5-(2-oxo-1,3-oxazolidine-4-ylméthyl)-1H-indole-3-yl]éthylamine ou un de ses sels, produits de solvatation ou dérivés physiologiquement fonctionnels, physiologiquement acceptable.

12. Composé suivant la revendication 10 ou la revendication 11, ou un de ses sels, produits de solvatation ou dérivés physiologiquement fonctionnels, physiologiquement acceptable, destiné à être utilisé comme agent thérapeutique.

13. Composé suivant la revendication 10 ou la revendication 11, ou un de ses sels, produits de solvatation ou dérivés physiologiquement fonctionnels, physiologiquement acceptable, destiné à être utilisé dans la prophylaxie ou le traitement d'un état pathologique pour lequel un agoniste des récepteurs "analogues à 5-HT_1", est indiqué.

14. Composé suivant la revendication 10 ou la revendication 11, ou un de ses sels, produits de solvatation ou dérivés physiologiquement fonctionnels, physiologiquement acceptable, destiné à être utilisé dans la prophylaxie ou le traitement de la migraine.